UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

NUTRITION 21,

Plaintiff,

v.

AMERICAN INTERNATIONAL CHEMICAL, INC.

Defendant.

Civil Action No.

00CV10004PBS

COMPLAINT

Nutrition 21, by way of complaint against the defendant alleges that:

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code.

THE PARTIES

2. Nutrition 21 is a limited partnership organized and existing under the laws of the State of California, having a place of business located at 1010 Turquoise Street, Suite 335, San Diego California 92109.

3. Upon information and belief, defendant American International Chemical, Inc. ("American") is a corporation organized and existing under the laws of the State of Massachusetts, having a principal place of business located at Strathmore Road, Natick, Massachusetts 01760.

JURISDICTION AND VENUE

4. Upon information and belief, American resides in this judicial district, is doing business in this judicial district, and is subject to the personal jurisdiction of this

5. This Court has jurisdiction over the subject matter of this action p

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AMOUNT $ 150.00
[illegible] Yes
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BY DPTY CLK JK
DATE 1-3-00

U.S.C. §1338(a).

6. Venue is proper in this district under 28 U.S.C. §1391(b) and (c) and §1400(b).

CLAIM FOR PATENT INFRINGEMENT

7. Paragraphs 1 through 6 are repeated as if fully set forth herein.

8. U.S. Patent No. Re. 33,988 was duly and legally issued on July 7, 1992 and is entitled "DIETARY SUPPLEMENTATION WITH ESSENTIAL METAL PICOLINATES" ("the '988 patent", Exhibit A hereto).

9. The United States of America as represented by the Secretary of Agriculture is the owner, by assignment, of all right, title and interest in and to the '988 patent.

10. Nutrition 21 is the exclusive licensee under the '988 patent for claims of the patent covering chromium picolinate, and is authorized by the owner of the '988 patent to bring this action for patent infringement (A copy of the License Agreement is attached hereto as Exhibit B).

11. Upon information and belief, American has made, sold, and/or offered for sale chromium picolinate within the United States, and/or has imported chromium picolinate into the United States, and/or has sold compositions containing chromium picolinate in the United States.

12. American has infringed one or more of the claims of the '988 patent, or else has contributed to and/or induced the infringement of the '988 patent by others, by making, selling and/or offering for sale chromium picolinate within the United States, and/or by importing chromium picolinate into the United States, and/or by making, selling and/or offering for sale compositions containing chromium picolinate in the United States.

13. American is on notice that its acts constitute infringement of the '988 patent.

14. The infringing acts committed by American are willful and wanton and will continue unless enjoined by this Court.

15. Nutrition 21 has been damaged by the infringing acts committed by American in an amount at least equal to $150,000, with the exact amount to be determined at trial. Nutrition 21's damages include the lost profits that it would have made on sales of its products embodying the claimed invention, but for the infringing acts committed by American, as well as a reasonable royalty adequate to compensate for the infringement. In addition, because the infringing acts committed by American have been willful, Nutrition 21 is entitled to treble damages and attorney's fees pursuant to 35 U.S.C. §§284 and 285.

16. The infringing acts committed by American have caused Nutrition 21 to suffer irreparable harm and injury. The infringement by American is in direct violation of Nutrition 21's rights under 35 U.S.C. §271 to exclude others from making, selling and/or offering for sale products embodying the invention of the '988 patent. Nutrition 21 has no adequate remedy at law and is likely to succeed on the merits of this Complaint. Nutrition 21 will continue to suffer irreparable harm unless an injunction is issued enjoining and restraining American from infringing the '988 patent.

RELIEF SOUGHT

WHEREFORE, plaintiff respectfully prays for judgment against defendant, as follows:

(a) that American has infringed the '988 patent;

(b) that an injunction issue permanently enjoining American and its agents, servants, and employees, and all those in active concert and participation with it, or any of them, from

infringing U.S. Patent No. Re. 33,988, including, without limitation, the manufacture, importation, acquisition, distribution, sale or offer for sale within the United States, of any chromium picolinate product embodying the invention claimed in the '988 patent;

(c) that an accounting be had, and judgment be rendered in Nutrition 21's favor, and against American for damages adequate to compensate for the infringement of the '988 patent, in an amount at least equal to $150,000, together with costs and interest, and that the Court treble said damages, as appropriate, and as authorized by Title 35 U.S. Code §284;

(d) that attorney's fees, costs and disbursements incurred in connection with the prosecution of this litigation be awarded to Nutrition 21;

(e) that Nutrition 21 be awarded pre-judgment interest; and

(f) for such other and further relief as the Court may deem just, proper and equitable under the circumstances.

Dated: Boston, Massachusetts
December 30, 1999

Steven Rosenthal

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Attorneys for Plaintiff

US00RE33988E

United States Patent [19]

Evans

[11] E Patent Number: Re. 33,988

[45] Reissued Date of Patent: Jul. 7, 1992

[54] DIETARY SUPPLEMENTATION WITH ESSENTIAL METAL PICOLINATES

[75] Inventor: Gary W. Evans, Puposky, Minn.

[73] Assignee: The United States of America as repesented by the Secretary of Agriculture, Washington, D.C.

[21] Appl. No.: 484,549

[22] Filed: Feb. 26, 1990

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 4,315,927
Issued: Feb. 16, 1982
Appl. No.: 176,234
Filed: Aug. 8, 1980

[51] Int. Cl.[5] A61K 31/555

[52] U.S. Cl. 514/188; 514/184

[58] Field of Search 514/188

[56] References Cited

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4,020,158	4/1977	Ashmead	424/177
4,021,569	5/1977	Abdel-Monem	424/289
4,167,564	9/1979	Jensen	424/177

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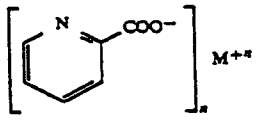
Primary Examiner—Sam Rosen

Attorney, Agent, or Firm—M. Howard Silverstein; John D. Fado; Curtis P. Ribando

[57] ABSTRACT

The levels of essential metals in the mammalian system can be precisely controlled by administering these metals in the form of exogenously synthesized coordination complexes of picolinic acid. The complexes are characterized by the following structural formula:



wherein M represents the metallic cation and n is equal to the cation's valence.

21 Claims, No Drawings

DIETARY SUPPLEMENTATION WITH ESSENTIAL METAL PICOLINATES

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The assimilation of an adequate quantity of physiologically important heavy metals is essential to the health of both humans and animals. Failure of the body to ingest and absorb the necessary amounts of such metals can lead to improper functioning of the metabolic processes as well as to a variety of diseases and associated symptoms. For example, anemia is correlated with an iron deficiency. Inadequate amounts of zinc may lead to skin conditions, loss of taste, neuropsychiatric symptoms, and in some animals the development of congenital anomalies and even the suppression of growth.

The absorptive cells of the mammalian intestine contain membranes and metal-binding proteins that present an ominous barrier to the transport of essential metal ions from the lumen to the blood. While metal deficiencies are often associated with improper dietary intake, they are also likely to be the result of malabsorption through this barrier. For instance, the infant disease acrodermatitis enteropathica (AE) impedes zinc absorption in the body, leading to death if not timely checked. This invention relates to a novel method of supplementing the diets of humans and animals with essential metals in an assimilable form which compensates for certain absorptive disorders.

2. Description of the Prior Art

Elemental metal and inorganic metallic salts have generally proven to be ineffective dietary amendments, particularly for subjects having intestinal malfunctions. Pharmacological doses of one metal can cause side effects resulting from competition with other metals. Also, the toxicity of these forms often restricts the dosages to suboptimal levels for attaining the desired profile in the organism's system.

More recent attempts to correct for metal deficiencies have concentrated on the use of organometallic compounds. Braun et al. [Europ. J. Pediat. 121: 247–261 (1976)] describes an attempt to treat AE in two children with 20 mg. Zn daily in the form of zinc-DL-aspartate, but with absolutely no clinical improvement. Ashmead et al., U.S. Pat. No. 4,020,158, employs metal proteinates as a feed supplement in which hydrolyzed protein products are chelated with metal ions under carefully controlled reaction conditions. Similarly, in U.S. Pat. No. 4,167,564, N. L. Jensen shows administering to animals essential metals as complexes or chelates with hydrolyzed proteins, wherein the complexes are stabilized by means of a buffer system. M. M. Abdel-Monem, U.S. Pat. No. 4,021,569, teaches zinc supplementation via zinc methionine complex salts.

While there is evidence that metals complexed with protein derivatives are more effectively assimilated than the elemental or inorganic salt forms, the exact mechanism of absorption, particularly as related to competing metals, has never been previously elucidated. Accordingly, there has always been some uncertainty attached to the prescription of proper dosages of supplemental elements.

SUMMARY OF THE INVENTION

I have now discovered that when selected essential metals as administered to mammals as exogenously synthesized coordination complexes of picolinic acid, they are directly available for absorption into the system without competition from other metals.

In accordance with this discovery, it is an object of the invention to provide a composition and method for selectively supplementing the essential metals in the diets of humans and mammalian animals, and for facilitating absorption of these metals by the intestinal cells.

It is also an object of the invention to correct predetermined metal deficiencies in mammals and to eliminate the symptoms of those deficiencies without concurrently reducing the assimilated levels of other essential metals.

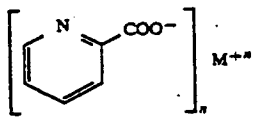
Another object of the invention is to administer trace elements in a safe, physiological form; that is, in the same form endogenously produced and utilized by the normal mammalian body. By so doing, deficiencies can be therapeutically eliminated without the need for pharmacological doses of metals, even when caused by intestinal malabsorption problems.

A further object of the invention is to administer supplemental metals in a form which is simple to produce and economically feasible to distribute on a commercial basis.

Other objects and advantages of this invention will become readily apparent from the ensuing description.

DETAILED DESCRIPTION OF THE INVENTION

The term "exogenously synthesized" as used herein is intended to distinguish the complexes of the invention from those which are endogenously produced by the body. The exogenously synthesized essential metal coordination complexes of picolinic acid (pyridine-2-carboxylic acid) for use in this invention are characterized by the following structural formula:



wherein M represents the metallic cation and n is equal to the cation's valence. The anionic picolinate moiety acts as a strong bidendate chelating agent, or ligand, capable of binding the cation. The cation may be any bivalent or trivalent metallic trace element essential to the nutritional well-being of humans or other mammalian species, provided that it exhibits a binding capacity with picolinic acid, as readily determined by a person in the art. Of particular interest are zinc, iron, and chromium, though it is envisioned that others such as copper, cobalt, and manganese would also be operable. These complexes are prepared by the simple method of adding picolinic acid to an aqueous solution of a water-soluble salt of the desired metal. Illustrative salts without limitation thereto are the sulfates, chlorides, and nitrates. In most cases the picolinates will crystallize from solution within about 24 hours under ambient conditions. However, it may be desirable to reduce the

temperature in order to hasten precipitation. The product may be purified by recrystallization, and then recovered and dried by any conventional procedure.

While the coordination complexes of this invention are intended primarily for oral ingestion, it is envisioned that they may also be injected directly into the gastrointestinal tract. When administered orally, they will generally be incorporated in the food material or drinking water. Alternatively, they may be manufactured into tablets or pills with a suitable diluent or carrier using any known technique.

The metal picolinates may be administered singly or in any combination. Insofar as the complexed cations are substantially 100% available to the mammalian system, supplementation may be limited to physiological amounts; that is, the quantity of metal which will actually be utilized by the body. In the case of a partial deficiency, the supplement need only contain a complementary amount of the deficient metal. For example, if the daily requirement of zinc were 5 mg. and the body was otherwise assimilating 2 mg., then an additional 3 mg. of zinc would be administered daily as zinc picolinate. For purposes of this invention, any dosage which will raise the metal level in the mammalian system to a predetermined value will be considered an effective amount or an effective dose.

While the applicant does not wish to be bound to any particular theory, it appears that when a metal is administered as the exogenously synthesized picolinate complex, it is transported from the intestinal lumen into the plasma by the same mechanism as dietary metal which is ligated in the intestinal tract by endogenous picolinic acid. The correlation between endogenous picolinic acid and zinc absorption has been previously reported by G. W. Evans et al. [Federal Proceedings 38: 703 (March 1979)] and G. W. Evans [Nutrition Reviews 38: 137–141 (1980)]. It now appears that when picolinic acid ligates other essential metals, it facilitates their absorption as well, even when exogenously synthesized. The primary advantage of the exogenous supplements of the invention is that they permit precise, preselected control over assimilation of the desired metals, and they are essentially immune to competition from other metals. An incidental and unexpected advantage is that by supplying exogenously synthesized picolinate complexes of one element, additional endogenous picolinic acid is sometimes available for facilitating the absorption of other dietary elements, thereby enhancing the overall essential metal profile of the system. Because the compounds of the invention have physiological counterparts, there is little question of their safety.

The following examples are intended only to further illustrate the invention and are not intended to limit the scope of the invention which is defined by the claims.

EXAMPLE 1

Preparation of Zinc Picolinate

Thirty grams of $ZnSO_4.7H_2O$ was dissolved in 200 ml. deionized water at room temperature. Thereafter, 20 g. picolinic acid (Sigma Chemical, St. Louis, MO) was added to the solution and the solution was stirred continuously. Within 3–5 minutes a precipitate began to form. After 30 minutes the stirring was discontinued and the mixture was left standing at room temperature until the precipitate had settled to the bottom. The supernatant was removed by aspiration and the precipitate was suspended in enough deionized water to yield 200 ml. This suspension was then heated in a beaker

with continuous stirring until the precipitate had completely dissolved after which the beaker was placed in an ice bath and stored overnight in a cold room (4°). The following morning the supernatant was aspirated from the crystals and the crystals were freeze dried. Assay of the crystals proved that the complex contained 2 moles of picolinic acid and 1 mole of zinc [zinc dipicolinate, $Zn(PA)_2$].

EXAMPLE 2

Preparation of Copper Picolinate

The procedure of Example 1 was repeated except that $CuSO_4.5H_2O$ was substituted for the zinc sulfate and recrystallization was facilitated by dissolving only small fractions of the precipitate in hot water at a time. The conversion of copper dipicolinate [$Cu(PA)_2$] was approximately 100%.

EXAMPLE 3

Preparation of Ferrous Picolinate

The procedure of Example 1 was repeated except for the following. Twenty grams of $FeSO_4.7H_2O$ was substituted for the zinc sulfate. When the picolinic acid was added, the solution turned red. The precipitate was recrystallized by dissolving it in 200 ml. of deionized boiling water followed by cooling in an ice bath. The ferrous dipicolinate [$Fe(PA)_2$] product was air dried.

EXAMPLE 4

Preparation of Chromium Picolinate

A solution was prepared by dissolving 512 mg. $CrCl_3.6H_2O$ (100 mg. Cr) and 750 mg. picolinic acid in 4.0 ml. deionized water. Crystals of chromium tripicolinate [$Cr(PA)_3$] formed after about 24 hours.

EXAMPLE 5

Zinc Supplementation of Pregnant and Lactating Dams

Female rats of the Long-Evans strain were bred and then transferred to individual stainless steel cages. They were fed Purina Lab Chow (Ralston Purina Co., St. Louis, MO) and deionized water for the first 14 days of gestation. Thereafter, the females were transferred to individual solid plastic cages and were fed ad libitum a purified basal diet (Table I) and a water solution that contained either zinc picolinate (10 μg. Zn/ml.) or zinc acetate (10 μg. Zn/ml.). The basal diet contained 8.5 μg. Zn/g. and 2 μg. pyridoxine-HCl/g.

Immediately after the pups were born, litter sizes were reduced to eight and these pups nursed for 5 days. At 1000 hours on the morning of the fifth day after birth, the pups were decapitated. The liver and kidneys were removed and freeze dried. The zinc concentration of these organs was determined by atomic absorption spectrometry (Varian, Model 1250) after the tissues had been digested in a mixture of nitric and sulfuric acids.

During the last week of gestation and the 5 days of lactation, there was no significant difference in either food consumption or supplemented water consumption between dams given zinc acetate and dams given zinc picolinate. Food consumption was 17.5±1.2 g./day for the dams in both groups. The dams given water supplemented with zinc acetate consumed 33.5±3.5 ml./day while the dams given the zinc picolinate supplement consumed 35.1±2.8 ml./day.

As shown in Table II, the zinc concentration of both the liver and the kidneys was significantly greater from

the pups suckling dams given the zinc picolinate supplement, indicating that zinc complexed with picolinic acid is transferred from the intestine of the lactating female to the pups much more readily than an organic zinc salt.

TABLE I

Composition of the Basal Diet

Ingredient	g./kg.
Sucrose[a]	624.6
Vitamin-free casein[b]	200
Corn oil[c]	90
Zinc-free salt mix[d]	26.9
Fibrous cellulose powder[e]	40
Vitamin ADE mix[f]	10
Rat vitamin mix[g]	5
Methionine[h]	2
Choline chloride[h]	1.5

[a]Jack Frost, National Sugar Refining Co., Philadelphia, PA.
[b]Teklad Test Diets, Madison, WI.
[c]Mazola, Best Foods, Englewood Cliffs, NJ.
[d]Bernhart and Tomarelli salt mixture with zinc omitted[J. Nutr. 89: 495–500(1966)]. Specially prepared Teklad Test Diets. The zinc content of the basal diet was 8.5 μg. Zn/g.
[e]Whatman CFII, W. and R. Balston Ltd., London, England.
[f]Vitamins were purchased from Nutritional Biochemicals Corp. The vitamin ADE mix contained 5.75 mg. ergocalciferol, 10 g. α-tocopherol, 2 g. retnyl palmitate, and corn oil to give a total weight of 1000 g.
[g]The rat vitamin mix contained 8 g. nincinamide, 5 g. calcium pantothenate, 1.6 g. riboflavin, 800 mg. thiamine hydrochloride, 400 mg. pyridoxine-HCl, 200 mg. folic acid, 30 mg. cyanocobalamine, 20 mg. menadione and sucrose to a final weight of 1000 g.
[h]Grand Island Biochemical Co., Grand Island, NY.

TABLE II

Zinc Concentration of Liver and Kidneys from Pups Nursing Dams Fed Zinc Supplement

Supplement to dam	Liver, μg. Zn/g. dry wt.	Kidneys, μg. Zn/g. dry wt.
Zinc acetate (n = 40)[a]	221 ± 52	92 ± 20
Zinc picolinate (n = 56)	276 ± 63[b]	125 ± 30[b]

[a]Number of pups shown in parenthesis. All values are mean ± S.D.
[b]Significantly greater ($P < 0.01$) than value obtained from pups nursing dams given the zinc acetate supplement. (Student's t-test).

EXAMPLE 6

The following clinical study has been reported in detail by I. Krieger in Nutrition Reviews 38(4): 148–150 (April 1980), herein incorporated by reference.

A 1-year-old human female suffering from the time that breastfeeding was stopped at 4 months from a variant form of acrodermatitis enteropathica, in which there was zinc dependency without hypozincemia, was maintained substantially symptom-free on an elemental zinc supplement of 45 mg./day until 20 months. During the few months which followed, intermittent treatments were interspersed with periods of reoccurring symptoms. At approximately 2 years, the patient was started on 60 mg. Zn^{++} (as zinc sulfate) and remained symptom-free for more than 2 years. Two attempts to lower the dosage to 30 mg. Zn^{++}/day were unsuccessful because of recurrent diarrhea.

At 4 years, she was started on 23.7 mg. zinc dipicolinate per day, diluted in water and divided into two doses of 5 ml. each. This amount of zinc dipicolinate contains 5 mg. Zn^{++} which is equivalent to the average intake of normal age controls. Assuming that the patient received a similar quantity of zinc in her diet, the total intake would have been 65 mg. Zn^{++} when on the zinc sulfate diet, and 10 mg. Zn^{++} during treatment with the picolinate. After 5 months, the patient remained symptom-free. Plasma zinc levels varied with the treatment as follows:

Treatment	Plasma zinc value (μg./deciliter)
none	120
$ZnSO_4$	172
$Zn(PA)_2$	148

An incidental and unexpected result was an increase in plasma copper level from 155 μg./deciliter during $ZnSO_4$ treatment to 251 μg./deciliter after 10 weeks of treatment with the picolinate. This is probably explainable on the basis that additional free intestinal picolinic acid was available to complex with the copper and thereby enhance its absorption.

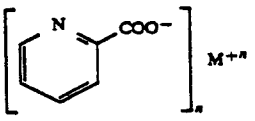
EXAMPLE 7

A 42-year-old human female having a history of iron deficiency anemia and suffering from exhaustion had been nonresponsive to pharmacological doses (about 60 mg./day or more) of iron in commercially available iron supplements. Blood analysis revealed a hematocrit of 31% and hemoglobin of 10.3 g./dl. She was started on 30 mg. ferrous dipicolinate per day. This supplement contained 5 mg. of elemental iron and was administered by mixing the powdered complex with a morning cup of coffee. During the course of supplementation she stated that she felt extremely energetic and after 12 days, her hematocrit increased to 36% and her hemoglobin increased to 12 g./dl. Discontinuation of the supplement on the 29th day led to a decrease in hemoglobin to 11.5 g./dl. These observations suggest that ferrous picolinate can effectively improve the iron profile in humans when administered at physiological levels.

It is understood that the foregoing detailed description is given merely by way of illustration and that modification and variations may be made therein without departing from the spirit and scope of the invention.

I claim:

1. A food composition for selectively supplementing essential metals in a mammalian diet and for facilitating absorption of said metals by the mammalian system comprising a food composition containing an effective amount of at least one exogenously synthesized essential metal picolinate complex characterized by the following structural formula:



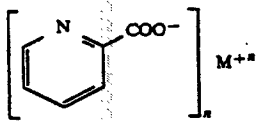
wherein M represents the metallic cation and n is equal to the cation's valence, *whereby said exogenously synthesized essential metal picolinate complex is supplemental to any endogenous essential metal picolinate present in said composition.*

2. The composition as described in claim 1 wherein said essential metal picolinate complex is zinc picolinate.

3. The composition as described in claim [1] *20* wherein said essential metal picolinate complex is ferrous picolinate.

4. A method for selectively supplementing essential metals in a mammalian diet and for facilitating absorp-

tion of said metals by the mammalian system comprising administering to said mammal an effective amount of an exogenously synthesized essential metal picolinate complex characterized by the following structural formula:



wherein M represents the metallic cation and n is equal to the cation's valence, *whereby said exogenously synthesized essential metal picolinate complex is supplemental to any endogenous essential metal picolinate present in said composition.*

5. The method as described in claim 4 wherein said essential metal picolinate complex is administered orally.

6. The method as described in claim 5 wherein said essential metal picolinate complex is administered as an aqueous solution.

7. The method as described in claim 5 wherein said essential metal picolinate complex is administered in combination with a food material.

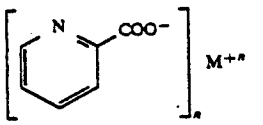
8. The method as described in claim 4 wherein said essential metal picolinate complex is zinc picolinate.

9. The method as described in claim [4] *21* wherein said essential metal picolinate complex is ferrous picolinate.

10. The method as described in claim 4 wherein said mammal is a human.

11. The method as described in claim 4 wherein said mammal is a domesticated animal.

12. A food composition for selectively supplementing an essential metal selected from the group consisting of iron, chromium, copper, cobalt, and manganese in a mammalian diet and for facilitating absorption of said metal by the mammalian system comprising a food composition containing an effective amount of at least one exogenously synthesized essential metal picolinate complex characterized by the following structural formula:



wherein M represents the cation of said metal and n is equal to the cation's valence.

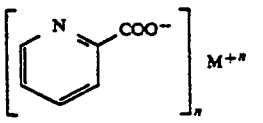
13. The composition as described in claim 12 wherein said essential metal picolinate complex is chromium picolinate.

14. The composition as described in claim 12 wherein said essential metal picolinate complex is copper picolinate.

15. The composition as described in claim 12 wherein said essential metal picolinate complex is cobalt picolinate.

16. The composition as described in claim 12 wherein said essential metal picolinate complex is manganese picolinate.

17. A method for selectively supplementing an essential metal selected from the group consisting of iron, chromium, copper, cobalt, and manganese in a mammalian diet and for facilitating absorption of said metal by the mammalian system comprising administering to said mammal an effective amount of an exogenously synthesized essential metal picolinate complex characterized by the following structural formula:



wherein M represents the cation of said metal and n is equal to the cation's valence.

18. The method as described in claim 17 wherein said essential metal picolinate complex is chromium picolinate.

19. The method as described in claim 17 wherein said essential metal picolinate complex is copper picolinate.

20. The method as described in claim 17 wherein said essential metal picolinate complex is cobalt picolinate.

21. The method as described in claim 17 wherein said essential metal picolinate complex is manganese picolinate.

* * * * *

LICENSE AGREEMENT

This Agreement is entered into between the National Technical Information Service (NTIS), a primary operating unit of the United States Department of Commerce, having offices at 5285 Port Royal Road, Springfield, VA 22161, and Nutrition 21 (LICENSEE), a California limited partnership, having offices in San Diego, California.

WHEREAS, the United States Department of Agriculture has sponsored research on dietary supplementation with essential metal picolinates and has received by assignment certain valuable patent rights thereon in the United States; and

WHEREAS, pursuant to 35 U.S.C. 207 and 37 C.F.R. 404, the Department of Agriculture has transferred custody of the entire right, title and interest in the patent rights to the Department of Commerce; and

WHEREAS, the Department of Commerce, pursuant to 35 U.S.C. 207 and 37 C.F.R. 404, is authorized to receive by transfer custody of the right, title and interest in federally owned inventions; to apply for, obtain and maintain patents on federally owned inventions in the United States and in foreign countries; to grant nonexclusive, partially exclusive or exclusive licenses under federally owned patents and patent applications; and to undertake all other suitable and necessary steps to protect and administer rights to federally owned inventions; and

WHEREAS, the Secretary of Commerce, through Department Organization Order 30-7A, has delegated to NTIS the authority of the Secretary to acquire federally owned inventions from other

Federal agencies for the purpose of licensing the use of those inventions in the United States; and

WHEREAS, NTIS desires, in the public interest, that the subject invention be perfected, marketed, and practiced so that the benefits are readily available for widest possible utilization in the shortest time possible; and

WHEREAS, LICENSEE has the facilities, personnel and expertise to bring, and is willing to expend reasonable efforts to bring the invention to the point of practical application at an early date.

NOW THEREFORE, in consideration of the foregoing including the above-cited patent licensing regulations, NTIS and LICENSEE agree as set forth below.

ARTICLE I

Definitions

1.1 Licensed Patent(s) shall mean U.S. Patent 4,315,927, issued February 16, 1982, and all reissues, renewals and extensions of such patent.

1.2 Licensed Product(s) shall mean a composition, encompassed within the scope of a claim in the Licensed Patent, for supplementing essential metals in the human diet.

1.3 Licensed Use shall mean a method, encompassed within the scope of a claim in a Licensed Patent, for supplementing essential metals in the human diet.

1.4 Net Sales shall mean the amount billed or invoiced on sales of Licensed Products or, in the event of disposal of any Licensed Products other than as scrap prior to its shipment from its place of manufacture or other than by sales, except for reasonable amounts of Licensed Products distributed as sales samples or for research, consistent with normal business practices, the amount billed or invoiced for a like quantity and quality of Licensed Products on or about the time of such disposal, less:

(a) Customary trade, quantity, or cash discounts and nonaffiliated brokers' or agents' commissions actually allowed and taken;

(b) Amounts repaid or credited by reason of rejections or returns; and/or

(c) Any freight or other transportation costs, insurance charges, duties, tariffs and all sales and excise taxes based directly on sales or turnover or delivery of material produced under this Agreement.

1.5 AFFILIATE shall mean any person, corporation, firm, partnership or other entity in which LICENSEE owns or controls at least fifty percent (50%) of the voting stock thereof.

1.6 Licensed Territory shall mean the United States, its territories, possessions and commonwealths.

ARTICLE II

Grant

2.1 NTIS hereby grants to LICENSEE and any AFFILIATES of LICENSEE's choice, subject to the terms and conditions herein, an exclusive license, under the Licensed Patent, to make, have made,

use and sell Licensed Products which do not contain zinc picolinate as their sole metal picolinate complex and to practice the Licensed Use with respect to such Licensed Products in the Licensed Territory, for a term beginning with the effective date of this Agreement and terminating on December 31, 1996. LICENSEE shall notify NTIS of any AFFILIATE included under this Paragraph 2.1.

2.2 NTIS hereby grants to LICENSEE and any AFFILIATES of LICENSEE's choice, subject to the terms and conditions herein, a nonexclusive license under the Licensed Patent to make, have made, use and sell Licensed Products which contain zinc picolinate as their sole metal picolinate complex and to practice the Licensed Use with respect to such Licensed Products for the duration of this Agreement.

2.3 NTIS hereby grants to LICENSEE and any AFFILIATES of LICENSEE's choice, subject to the terms and conditions herein, a nonexclusive license under the Licensed Patent to make, have made, use and sell Licensed Products which do not contain zinc picolinate as their sole metal picolinate complex and to practice the Licensed Use, with respect to such Licensed Products in the Licensed Territory after the expiration of the exclusive license term mentioned in Paragraph 2.1 above and extending for the remaining term of this Agreement. LICENSEE shall notify NTIS of any AFFILIATE included under this Paragraph 2.3.

2.4 NTIS hereby grants to LICENSEE the right to grant sublicenses to nonaffiliated companies subject to the provisions of this Agreement and to the submission to, and approval by NTIS of the proposed sublicense, which approval shall not be unreasonably withheld. Each sublicense shall make reference to this

4.2 (a) LICENSEE shall also pay to NTIS an annual maintenance fee of One Thousand Dollars ($1,000), no part of which shall be refunded for any reason. The first annual maintenance fee payment which shall be paid at the time of making the payment required in Paragraph 4.1 above, shall be prorated for the balance of the calendar year remaining after the effective date of this Agreement. Subsequent annual maintenance fees shall accrue on January 1 of each year and shall be payable within sixty (60) days thereafter during the term of this Agreement. Should the cost to NTIS for ordinary and usual procedures for obtaining and maintaining any Licensed Patent(s) exceed in any year the total annual maintenance fee received from LICENSEE under the Licensed Patent(s), NTIS may request LICENSEE to increase its minimum annual fee in subsequent years to cover such excess costs. Should LICENSEE fail to include such increased amount when requested by NTIS and due, NTIS may terminate LICENSEE's license under such Licensed Patent(s) in accordance with the provisions of Paragraph 9.2 hereof. The annual maintenance fee paid by LICENSEE for any given year shall be a credit against any administration and royalty fee accrued for such year in accordance with Paragraph 4.3 below. The administration and royalty fee accrued in any one calendar year shall not be credited against the annual maintenance fee paid or to be paid in any other year.

(b) Before any commitment to expend substantial funds for an extraordinary and unusual procedure for obtaining and maintaining any Licensed Patent(s), including but not limited to interference, reissue, term-extension and reexamination but not including infringement or counterclaims thereto, NTIS shall notify LICENSEE of such extraordinary and unusual procedure and the estimated cost thereof and request LICENSEE to assume responsibility for such cost. Should LICENSEE decline to assume

Agreement including the rights retained by the Government and a copy of such sublicense shall be furnished to NTIS promptly after its execution.

2.5 NTIS hereby grants to LICENSEE and its included AFFILIATES and sublicensees the right to extend to their customers of Licensed Products on which an administration and royalty fee has been or will be paid the right to use such Licensed Product for the Licensed Use.

ARTICLE III

Reservation of Rights

3.1 The licenses granted in Article II above are subject to the reservation by NTIS of an irrevocable, nonexclusive, nontransferable, royalty-free license for the practice of all inventions encompassed within the Licensed Patents throughout the world by and on behalf of the Government of the United States and on behalf of any foreign government or international organization pursuant to any existing or future treaty or agreement to which the United States is signatory, including the right to engage in research on inventions included under the Licensed Patents either alone or with one or more third parties.

3.2 NTIS reserves the right to require LICENSEE to grant sublicenses to responsible applicants on reasonable terms when necessary to fulfill health or safety needs.

ARTICLE IV

Royalties and Payments

4.1 Within thirty (30) days after the execution date of this Agreement by NTIS, LICENSEE shall pay to NTIS an execution fee of Three Thousand Dollars ($3,000), no part of which shall be refunded for any reason.

such responsibility, NTIS may terminate LICENSEE's license under such Licensed Patent(s) in accordance with the provisions of Paragraph 9.2 hereof.

(c) With respect to the excess costs mentioned in Paragraphs 4.2(a) and (b) above, during the exclusive term of this Agreement, LICENSEE shall be requested to pay the full amount of such costs and during the nonexclusive term of this Agreement, LICENSEE shall be requested to pay a pro-rated share of such costs, i.e. the total cost divided equally among all licensees under the Licensed Patents.

4.3 LICENSEE shall pay NTIS an administration and royalty fee on the Net Sales of LICENSEE and its included AFFILIATES and sublicensees of three percent (3%) during the exclusive period of this Agreement and of two percent (2%) during the nonexclusive period of this Agreement.

4.4 No administration and royalty fee shall be payable hereunder for direct sales of Licensed Products by LICENSEE or its included AFFILIATES and sublicensees to the Government of the United States of America or on any Licensed Product scrapped prior to shipment from its place of manufacture.

4.5 LICENSEE agrees to submit to NTIS within sixty (60) days after each calendar half year ending June 30th and December 31st, reports setting forth for the preceding six (6) month period the amount of Licensed Product made, used, sold or otherwise disposed of (except scrap as previously provided) by LICENSEE and its included AFFILIATES and sublicensees in the Licensed Territory, the Net Sales thereof separated as to Net Sales within the Licensed Territory and those of Licensed Product made within the Licensed Territory but sold elsewhere and the

amount of administration and royalty fee due thereon, and with each such report, LICENSEE agrees to pay the amount of such fee due. If no such fee is due to NTIS for any report period, the written report shall so state.

4.6 All payments due NTIS under this Article IV shall be payable in United States dollars for the account of "NTIS/Patent Licensing." All checks and bank drafts shall be drawn on United States banks. If payments are overdue, late charges will be applied as required by the Department of Treasury (Treasury Fiscal Requirements Manual, Section 8020.20). Conversion of foreign currency to United States dollars shall be made at the conversion rate existing in the United States on the last business day of the applicable reporting period for the purchase of United States dollar bank wire transfers for settlement of such payment obligations. Any and all loss of exchange, value, taxes, or other expenses incurred in the transfer or conversion of other currency to United States dollars shall be paid entirely by LICENSEE.

4.7 LICENSEE and/or its included AFFILIATES and/or sublicensees shall pay all necessary expenses for its commercialization of Licensed Products and such expenses shall not be deducted from any payments due NTIS as provided herein.

ARTICLE V

Markings

LICENSEE, its included AFFILIATES and sublicensees may, at their sole option and in conformity with applicable statutes, identify Licensed Products with the marking "Licensed Under U.S. Patent 4,315,927." The name of the Government employee inventor, the name of any agency or department of the United States

Government, or any adaptation of the above shall not be used in any promotional activity without prior written approval from NTIS.

ARTICLE VI

Reports and Royalty Payments

6.1 LICENSEE shall provide written annual reports within sixty (60) days of the end of each calendar year detailing progress being made to bring the invention licensed hereunder to practical application. No further annual progress reports will be required after notification of the first commercial sale of Licensed Products unless otherwise requested by NTIS.

6.2 LICENSEE, and its included AFFILIATES shall keep and shall cause their sublicensees to keep accurate and complete records of Licensed Products made, used, sold or otherwise disposed of (except scrap as previously provided) under this Agreement in the Licensed Territory, appropriate to determine the amount of the administration and royalty fee due hereunder. Such records shall be retained for at least two (2) years following a given reporting period and, upon reasonable notice, shall be available during normal business hours for inspection at the expense of NTIS by an accountant selected by NTIS and approved by LICENSEE for the sole purpose of verifying reports and payments hereunder. Such accountant shall not disclose to NTIS any information other than information relating to the accuracy of reports and payments made under this Agreement.

ARTICLE VII

Patent Enforcement

7.1 LICENSEE shall notify NTIS promptly in writing of any infringement of a Licensed Patent which becomes known to

LICENSEE. If NTIS determines that a substantial infringement exists, NTIS shall communicate such determination to LICENSEE in writing and take prompt action to attempt to eliminate that substantial infringement. LICENSEE shall cooperate with NTIS in determining if substantial infringement exists and, if so, in attempting to eliminate that substantial infringement.

7.2 During the exclusive term of this Agreement, as provided under Paragraph 2.1 above, LICENSEE is empowered pursuant to the provisions of Chapter 29 of Title 35, United States Code or other statutes:

(a) to bring suit in its own name, at its own expense, and on its own behalf for infringement of presumably valid claims in a Licensed Patent;

(b) in any such suit, to enjoin infringement and to collect for its use, damages, profits, and awards of whatever nature recoverable for such infringement; and

(c) to settle any claim or suit for infringement of the Licensed Patent.

provided, however, that NTIS and appropriate U.S. Government authorities shall have a continuing right to intervene in such suit.

7.3 If NTIS receives LICENSEE's infringement notice under the provisions of paragraph 7.1 above during the nonexclusive term of this agreement, as provided under Paragraphs 2.2 and 2.3 above, and within a reasonable time following the date of such notice, NTIS is unsuccessful in eliminating the infringement which it has determined is substantial, NTIS agrees to recommend to the appropriate United States Government authorities that an infringement action based on such infringed Licensed Patent be initiated. LICENSEE shall, at NTIS' request, cooperate in every

respect in the preparation and prosecution of such action including making available to NTIS records, information, evidence, and testimony by employees of LICENSEE relevant to the substantial infringement of the Licensed Patent.

7.4 If, after twelve (12) months from the date of LICENSEE's notice of an infringement mentioned in Paragraph 7.3 above, which infringement NTIS has determined constitutes a substantial infringement of a Licensed Patent and NTIS has not eliminated such substantial infringement and the United States Government has not initiated an infringement suit, LICENSEE shall be excused from payment of the administration and royalty fee due hereunder resulting from sales or other disposition of Licensed Products in the country in which the substantial infringement exists. When the substantial infringement has been eliminated or an infringement suit has been initiated, NTIS shall notify LICENSEE in writing of either of such event and LICENSEE's obligation to pay the administration and royalty fee shall resume as of the date that the infringement is eliminated or such infringement suit is initiated.

ARTICLE VIII

Licensee Performance

8.1 LICENSEE shall expend reasonable efforts and resources to carry out the development and marketing plan submitted with LICENSEE's application for a license and to bring Licensed Products to the point of practical application [as defined at 37 C.F.R. 404.3(d)] within one (1) year of the effective date of this Agreement, unless this period is extended by mutual agreement of the parties. NTIS shall not unreasonably withhold approval of any request of LICENSEE to extend this period, if such request is supported by a reasonable showing by LICENSEE of

due diligence toward bringing the Licensed Products to the point of practical application. "Due diligence" shall include any reasonable and diligent application for approval required by any Government agency within the United States.

8.2 After bringing Licensed Products to the point of practical application in the Licensed Territory, LICENSEE agrees to keep Licensed Products reasonably available to the public in the Licensed Territory during the term of this Agreement.

8.3 LICENSEE agrees that Licensed Products sold or otherwise disposed of in the Licensed Territory by LICENSEE, its included AFFILIATES and sublicensees will be manufactured substantially in the Licensed Territory.

8.4 Failure to comply with the terms of this Article VIII shall be cause for modification or termination of this Agreement in accordance with the provisions of Article IX below.

ARTICLE IX

Modification and Termination

9.1 This Agreement may be modified or terminated by NTIS subject to the provisions of Paragraphs 9.2 and 11.4 below, if it is determined that:

(a) LICENSEE or any of its included AFFILIATES or any of its sublicensees fail to meet the obligations set forth in Article VIII above;

(b) Such action is necessary to meet requirements for public use specified by Federal regulations issued after the date of the license and such requirements are not reasonably satisfied by the LICENSEE, its included AFFILIATES or its sublicensees;

(c) LICENSEE has willfully made a false statement of or willfully omitted a material fact in the license application or in any report required by this Agreement;

(d) LICENSEE or any of its included AFFILIATES or any of its sublicensees commit a substantial breach of a covenant or agreement contained in this Agreement;

(e) LICENSEE is adjudged a bankrupt or has its assets placed in the hands of a receiver or makes any assignment or other accommodation for the benefit of creditors; or

(f) LICENSEE or any of its included AFFILIATES or any of its sublicensees misuse the Licensed Patent or misrepresent in any promotional activity the therapeutic or dietary value of human consumption of any Licensed Product.

9.2 Prior to any modification or termination of this Agreement, NTIS shall furnish LICENSEE and any sublicensees of record a written notice of intention to modify or terminate, and the LICENSEE and any notified sublicensee shall be allowed thirty (30) days after the date on such notice to remedy any breach or default of any covenant or agreement of this Agreement or to show cause why this Agreement should not be modified or terminated.

9.3 LICENSEE may terminate this Agreement at any time as to any or all Licensed Patents upon ninety (90) days written notice to NTIS.

9.4 Upon termination of this Agreement, sums due to NTIS from LICENSEE in respect of the Licensed Patent(s) included in such termination shall become immediately payable. In all other

respects, the right and obligations of the parties hereto concerning the Licensed Patent(s) included in such termination shall cease as of the effective date of such termination.

9.5 In the event of termination of this Agreement, any sublicense of record granted pursuant to Paragraph 2.3 may, at sublicensee's option be converted to a license directly between sublicensee and NTIS.

ARTICLE X

Duration

This Agreement, unless sooner terminated as provided herein, shall remain in effect until the expiration of the last-to-expire Licensed Patent.

ARTICLE XI

General

11.1 NTIS represents and warrants that the entire right, title and interest in the Licensed Patent(s) has been assigned to the United States of America as represented by the Secretary of Commerce and that NTIS has the authority to issue licenses under the Licensed Patent(s). NTIS does not warrant the patentability or validity of the Licensed Patent(s) and makes no representations whatsoever with regard to the scope of the Licensed Patent(s) or that such Licensed Patent(s) may be exploited without infringing other patents.

11.2 This Agreement may not be transferred or assigned by LICENSEE to any party other than to a successor or assignee of the entire business interest of LICENSEE relating to Licensed Products.

11.3 NTIS shall notify LICENSEE of any subsequent agreement containing more favorable terms and conditions which may hereafter be granted by NTIS to any other party under the Licensed Patent(s), and LICENSEE, if it is in a position to do so, may substitute all the terms and conditions of such other agreement for the terms and conditions of this Agreement.

11.4 The parties shall make every reasonable effort to resolve amicably any dispute concerning a question of fact arising under this Agreement. Any disputes not settled amicably between the parties concerning a question of fact arising under this Agreement shall be decided by the Director, NTIS, who shall reduce his decision to writing and mail or otherwise furnish a copy thereof to LICENSEE. The decision of the Director, NTIS, to modify or terminate this Agreement shall be final and conclusive unless LICENSEE mails or otherwise furnishes to the Director, NTIS, a written appeal under the Appeal Procedures of 15 C.F.R. Part 17, Subpart C. Pending final decision of a dispute hereunder, LICENSEE shall proceed diligently with the performance of its obligations under this Agreement.

11.5 The interpretation and application of the provisions of this Agreement shall be governed by the laws of the United States as interpreted and applied by the Federal courts in the District of Columbia.

11.6 Written notices required to be given under this Agreement shall be considered duly given if mailed by first class mail, postage prepaid and addressed as follows:

If to NTIS: Director, Office of Federal Patent Licensing
National Technical Information Service
United States Department of Commerce
5285 Port Royal Road
Springfield, VA 22161

If to LICENSEE: President
Nutrition 21
1010 Turquoise Street
Suite 335
San Diego, CA 92109

or such other address as either party may request in writing.

11.7 This Agreement constitutes the entire understanding and supersedes all prior agreements and understandings between the parties with respect to the subject matter hereof or information relating thereto except for any non-disclosure agreement relating to the claims of the Licensed Patent(s) which non-disclosure agreement, if any, is incorporated herein by reference, and neither party shall be obligated by any condition, promise or representation other than those expressly stated herein or as may be subsequently agreed to by the parties hereto in writing.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their duly authorized representatives.

The effective date of this Agreement is January 1, 1987.

Witness:
Mary Lou J. Campion

National Technical Information Service
Joseph F. Caponio
JOSEPH F. CAPONIO
Director

January 12, 1987
Date

January 12, 1987
Date

Witness:
Bonnie L. Ricci

Nutrition 21
James E. Lee
(By)
President
(Title)

12/2/86
Date

12-2-86
Date

United States Department of Agriculture
Agricultural Research Service
Office of the Administrator
Washington, D.C. 20250

Reply to: Office of Technology Transfer
Room 415, Bldg. 005, BARC-W
Beltsville, Maryland 20705-2350
Phone: 301-504-5989
Fax: 301-504-5060

VIA FAX AND MAIL

October 23, 1996

IN REPLY
REFER TO: License for U.S. Patent Re 33,988, Reissue of U.S. Patent No. 4,315,927 (S.N. 06/176,234), "Dietary Supplementation with Essential Metal Picolinates"

Mr. Jeff Korber
Executive Vice President
Nutrition 21
1010 Turquoise Street, Suite 335
San Diego, California 92109

Dear Mr. Korber:

I am responding to your letter dated September 27 concerning the term of the above referenced license agreement. Pursuant to Paragraph 1.1 of the agreement, the license granted includes all extensions of the licensed patent. Due to recent changes in the patent statute, the term of the licensed patent has been extended from February 16, 1999 to August 8, 2000.

The license agreement was amended in January of 1993 to extend the period of exclusivity from December 31, 1996 to February 16, 1999. In other words, the exclusive period was extended to the full term of the licensed patent that was possible at the time the amendment was executed. Therefore, it is consistent with the intent of the agreement that period of exclusivity be extended to the full term of the licensed patent, which will expire August 8, 2000.

Please give me a call if you have any questions, or if you need any additional information.

Sincerely,

June Blalock

JUNE BLALOCK
Coordinator
Technology Licensing Program

cc: R. Parry H. Silverstein

Agricultural Research Service

NUTRITION 21
CHROMAX® SELENOMAX® ZINMAX®
A Limited Partnership

1010 Turquoise Street, Suite 335
San Diego, California 92109-1268
619/488-1021
Fax 619/488-7316

General Partner: Selene Systems, Inc.
A California Corporation

September 27, 1996

Ms. June Blalock
United States Department of Agriculture
Office of Technology Transfer
Room 416 Bldg. 005, BARC-W
Beltsville, ND 20705-2350

Dear June:

Re: Licenses on S.N. 06/176,234 #1 and reissued on July 7, 1992, as Re. 33,988.

It was a pleasure to talk with you regarding our chromium picolinate license. It is my understanding that your patent attorney indicated that the extension of our patent by GATT from February 8, 1999 to August 8, 2000 triggers an automatic extension of our license with NTIS for the identical period.

I would greatly appreciate a letter from the appropriate party confirming this understanding.

Sincerely,

Jeff Korber, J.D.
Executive Vice President

cc: Lowell Andersen
Knobbe, Martens, Olson & Bear

/mt